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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/033,244	12/27/2001	David Botstein	P2930R1C2	1015

7590 06/21/2005

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EXAMINER	
FREDMAN, JEFFREY NORMAN	
ART UNIT	**PAPER NUMBER**
1637	

DATE MAILED: 06/21/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/033,244	BOTSTEIN ET AL.	
	Examiner	Art Unit	
	Jeffrey Fredman	1637	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on 27 December 2004 .

2a)☒ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) 22-27 is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) 22-27 is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) 5/05
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on May 16, 2005 has been entered.

Claim Rejections - 35 USC § 101

2. 35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

3. Claims 22-27 are rejected under 35 U.S.C. 101 because the claimed invention lacks patentable utility.

The current claims are drawn to a genus of antibodies which bind to a protein termed PRO1800 in the specification.

Credible Utility

Following the requirements of the Utility Guidelines (See: Federal Register: December 21, 1999 (Volume 64, Number 244), revised guidelines for Utility.), the first inquiry is whether a credible utility is cited in the specification for use of the proteins. The cited utilities in the specification are that the protein is related to the Hep27 protein, which the specification states may be involved in some DNA synthesis related pathway.

There is some evidence of overexpression in certain lung tumors (but not in others) at page 117. These utilities are credible.

Upon identification of credible utilities, the next issue is whether there are any well established utilities for the protein. No well established utilities for this specific PRO1800 protein, antibody or nucleic acid are identified in either the specification or in the cited prior art.

Substantial utility

Given the absence of a well established utility, the next issue is whether substantial utilities are disclosed in the specification. Here, the evidence in the specification provided is that the protein is related by homology to the Hep 27 protein. This relationship lacks any of the hallmarks of utility. The homology does not imply that the proteins are similar in any function way, or that they are expressed in similar tissue types or under similar conditions. There is no biological activity, expression pattern, phenotype, disease or condition, ligand, binding partner or any other specific feature which is disclosed as being associated with PRO1800. Without any further information, there is no expectation that the protein will have any properties in common with the Hep 27 protein. There is an abundance of evidence that very similar proteins can perform very different functions. For example, Rost et al (J. Mol. Biol. (2002) 318(2):595-608) notes regarding assignment of enzymatic activity based upon homology comparisons that "The results illustrated how difficult it is to assess the conservation of protein function and to guarantee error-free genome annotations, in general: sets with millions of pair comparisons might not suffice to arrive at statistically significant conclusions

(abstract)." Thus, even high levels of homology do not necessarily correlate with actual protein function. In the current case, where not only is the function of PRO1800 not known, but no specific function has been definitively identified for the related Hep 27 protein itself, the expectation is even lower that there is any utility that can be derived based upon this association.

As noted in the utility guidelines, basic research on a product to identify properties and intermediate products which themselves lack substantial utility are all insubstantial utilities (see page 6 of the Utility guideline training materials). First, there is NO data in the specification showing association of PRO1800 with any disease state. The Examiner notes additional art that supports the rejection, in that the art indicates that a two-fold amplification at the DNA level would not be expected to be predictive of protein amplification.

Hu et al. (2003, Journal of Proteome Research 2:405-412) analyzed 2286 genes that showed a greater than l-fold difference in mean expression level between breast cancer samples and normal samples in a microarray (p. 408, middle of right column) and discovered that, for genes displaying a 5-fold change or less in tumors compared to normal, there was no evidence of a correlation between altered gene expression and a known role in the disease. However, among genes with a 10-fold or more change in expression level, there was a strong and significant correlation between expression level and a published role in the disease (see discussion section).

Hanna et al. (Pathology Associates Medical Laboratories, 1999) show that gene amplification does not reliably correlate with polypeptide over-expression, and thus the

level of polypeptide expression must be tested empirically. The instant specification does not provide this additional information, and thus the skilled artisan would need to perform additional experiments. Since the asserted utility for the claimed polypeptides is not in currently available form, the asserted utility is not substantial.

Orntoft et al. (Molecular and Cellular Proteomics1:37-45, 2002) could only compare the levels of about 40 well-resolved and focused abundant proteins." (See abstract.) It would appear that applicants have provided no fact or evidence concerning a correlation between such low levels of amplification of DNA, found only in a minority of tested tumors which were not characterized on the basis of those in the Orntoft publication, and an associated rise in level of the encoded protein.

Hyman (Cancer Research 62:6240-6245) found 44% of highly amplified genes showing overexpression at the mRNA level, and 10.5% of highly overexpressed genes being amplified; thus, even at the level of high amplification and high overexpression, the two do not correlate. Further, the article at page 6244 states that of the 12,000 transcripts analyzed, a set of 270 was identified in which overexpression was attributable to gene amplification. This proportion is approximately 2%; the Examiner maintains that 2% does not provide a reasonable expectation that the slight amplification of PRO1800 would be correlated with elevated levels of mRNA, much less protein. Hyman does not examine protein expression.

Second, the overexpression data does not provide a substantial utility for several reasons. First, there is no showing that the overexpression was statistically significant and correlated with any diagnostic utility. The absence of such a diagnostic utility is

particularly striking since there is no evidence that the overexpression effect was statistically significant, that the effect was reproducible, or that the effect was anything other than a nonspecific effect due to the presence of an exogenous protein in the mixture. Finally, the claims at issue are drawn to antibodies. In the current case, there is no evidence that the protein is expressed in any particular tissue type. There is no evidence that the protein is overexpressed in cancerous cells, or that the protein has any utility whatsoever. As numerous references show, there is no necessary relationship between nucleic acid expression in a cell and protein expression. For example, Pennica et al (Proc. Natl. Acad. Sci. (1998) 95:14717-14722) shows that the Wisp-2 DNA was amplified by the RNA expression was reduced in tumors (see abstract). Konopka (Proc. Natl. Acad. Sci. (1986) 83:4049-4052) states that "Protein expression is not related to amplification of the abl gene but to variation in the level of bcr-abl mRNA produced from a single Ph1 template. (see abstract)." So even if there is a gene amplification, that would provide no utility whatsoever for the protein or antibody, since the gene amplification does not necessarily relate to the expression information of the protein and cognate antibody.

Third, the art supports the conclusion that many genes are irrelevant in gene microarray assays. As Li et al (J. Theoretical Biology (2002) 219:513-551) note "The presence of this power law function prevents an intrinsic cutoff point between "important" genes and "irrelevant" genes (see abstract)." Li continues in the text to note that "In a typical microarray experiment, however, the problem is not that one does not put enough genes on a chip, but rather having too many genes (see page 539, column

1)." This concept that genes whose expression does not change is irrelevant is not limited to Li. Ding et al (Bioinformatics (2003) 19(10):1259-66) notes "A two-way ordering of gene expression data can force irrelevant genes toward the middle in the ordering and can thus be discarded (See abstract)." So Ding expressly indicates that genes without change in expression profiling (and Ding's preferred embodiment is cancer genes) should be discarded. Ding notes at page 1259 that in a selection from thousands of genes, 50 are sufficient. Similarly, Sawiris et al (Cancer Research (2002) 62:2923-2928) notes "One of the advantages of specialized arrays is that they do not include irrelevant genes that may contribute to noise during data analysis (see page 2923, column 2)." Thus, the overwhelming state of the art supports the position that many genes are irrelevant, that genes whose expression does not change are noise, and that these irrelevant genes are so insignificant that ideally they are not placed on the arrays or used at all. Therefore, such genes lack substantial utility as useful on gene expression arrays.

Even Applicant's newly cited reference, Smith et al (WO 97/38085) notes the unpredictability of gene overexpression studies by differential display, stating

> "Despite the advancement provided by differential display, problems remain in terms of applying it in the search for new cancer genes. First, because this is a test for RNA levels. any phenotypic difference between cell lines constitute part of the recovered set, leading to a large proportion of "false positive" identifications. It has been found that cDNA for mitochondrial genes
> constitute a large proportion of the differentially expressed bands, and it consumes substantial resources to recover the sample and obtain a partial sequence in order to eliminate them. Second,

> false positive identications are made for reasons attributed to multiple cDNA species and competition for the PCR primers by RNA species of different abundance (Debouck). Third, differential display highlights high copy number mRNAs and shorter mRNA (Bertioli et al., Yeatman et al.), and may therefore miss critical cancer-asseated transcripts when used as a survey technique. Fourth, a number of adjustments are made to gene expression levels when a cell undergoes malignant transformation or cultured in vitro. Most of these adjustments are secondary, and not part of the transformation process. Thus, even when a novel sequence is obtained from the differential display, it is far from certain that the corresponding gene is at the root of the disease process. (see page 4)."

This is an express teaching that simply testing for RNA levels does not provide diagnostic information regarding any particular mRNA found because a large proportion of the RNAs shown to have differences are "false positives." Thus, any particular novel sequence which is identified as overexpressed is more likely to be false positive than not.

Specific Utility

In the current case, even if the substantial utility argument above were found unpersuasive, there is no specific utility given for this protein and resultant nucleic acid. The protein has not been associated with any disease, any condition, any enzymatic activity or any other specific feature. The only association is that it has some homology to a protein, Hep 27, which is associated with DNA synthesis in some undefined way. As the utility guideline training materials note on page 5-6, "Similarly, a general statement of diagnostic utility, such as diagnosing an unspecified disease, would ordinarily be insufficient absent a disclosure of what condition can be diagnosed". Here,

there is no disclosure of any condition which can be diagnosed and hence, no specific utility.

Finally, with regard to the utility analysis, the current situation directly tracks Example 4 of the utility guidelines, where a protein of entirely unknown function was characterized as lacking utility.

Claim Rejections - 35 USC § 112 – Enablement

4. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

5. Claims 22-27 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Factors to be considered in determining whether a disclosure meets the enablement requirement of 35 USC 112, first paragraph, have been described by the court in In re Wands, 8 USPQ2d 1400 (CA FC 1988). Wands states at page 1404,

> "Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized by the board in Ex parte Forman. They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or

absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims."

The nature of the invention

The claims are drawn to antibodies which bind the PRO1800 protein. The invention is in a class of invention which the CAFC has characterized as "the unpredictable arts such as chemistry and biology." Mycogen Plant Sci., Inc. v. Monsanto Co., 243 F.3d 1316, 1330 (Fed. Cir. 2001).

The breadth of the claims

The claims broadly encompass any antibody which binds to the PRO1800 protein and also include any antibody fragments which bind to the PRO1800 protein.

Quantity of Experimentation

The quantity of experimentation in this area is extremely large since there is significant variability in the activity of polypeptides and antibodies. It would require significant study to identify the actual function of the PRO1800 protein, and identifying a use for this protein would be an inventive, unpredictable and difficult undertaking in itself. This would require years of inventive effort, with each of the many intervening steps, upon effective reduction to practice, not providing any guarantee of success in the succeeding steps.

The unpredictability of the art and the state of the prior art

The art is extremely unpredictable with regard to protein function in the absence of reliable information regarding the protein activity. Even very similar proteins, as

shown by homology, may have very different functions (see Rost et al (J. Mol. Biol. (2002) 318(2):595-608). In the current case, where no specific information is known regarding the function of the protein in actual biological organisms, it is entirely unpredictable what function and activity will be found for this protein. The prior art does not resolve this ambiguity, since no prior art activity is identified for the protein.

Further, the art supports the conclusion that many genes are irrelevant in gene microarray assays. As Li et al (J. Theoretical Biology (2002) 219:513-551) note "The presence of this power law function prevents an intrinsic cutoff point between "important" genes and "irrelevant" genes (see abstract)." Li continues in the text to note that "In a typical microarray experiment, however, the problem is not that one does not put enough genes on a chip, but rather having too many genes (see page 539, column 1)." This concept that genes whose expression does not change is irrelevant is not limited to Li. Ding et al (Bioinformatics (2003) 19(10):1259-66) notes "A two-way ordering of gene expression data can force irrelevant genes toward the middle in the ordering and can thus be discarded (See abstract)." So Ding expressly indicates that genes without change in expression profiling (and Ding's preferred embodiment is cancer genes) should be discarded. Ding notes at page 1259 that in a selection from thousands of genes, 50 are sufficient. Similarly, Sawiris et al (Cancer Research (2002) 62:2923-2928) notes "One of the advantages of specialized arrays is that they do not include irrelevant genes that may contribute to noise during data analysis (see page 2923, column 2)." Thus, the overwhelming state of the art supports the position that many genes are irrelevant, that genes whose expression does not change are noise,

and that these irrelevant genes are so insignificant that ideally they are not placed on the arrays or used at all. Therefore, such genes lack substantial utility as useful on gene expression arrays.

The Examiner notes additional art that supports the rejection, in that the art indicates that a two-fold amplification at the DNA level would not be expected to be predictive of protein amplification.

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> "Despite the advancement provided by differential display, problems remain in terms of applying it in the search for new cancer genes. First, because this is a test for RNA levels. any phenotypic difference between cell lines constitute part of the recovered set, leading to a large proportion of "false positive" identifications. It has been found that cDNA for mitochondrial genes
> constitute a large proportion of the differentially expressed bands, and it consumes substantial resources to recover the sample and obtain a partial sequence in order to eliminate them. Second, false positive identications are made for reasons attributed to multiple cDNA species and competition for the PCR primers by RNA species of different abundance (Debouck). Third, differential display highlights high copy number mRNAs and shorter mRNA (Bertioli et al., Yeatman et al.), and may therefore miss critical cancer-asseated transcripts when used as a survey technique. Fourth, a number of adjustments are made to gene expression levels when a cell undergoes malignant transformation or cultured in vitro. Most of these adjustments are secondary, and not part of the transformation process. Thus, even when a novel sequence is obtained from the differential display, it is far from certain that the corresponding gene is at the root of the disease process. (see page 4)."

This is an express teaching that simply testing for RNA levels does not provide diagnostic information regarding any particular mRNA found because a large proportion of the RNAs shown to have differences are "false positives." Thus, any

particular novel sequence which is identified as overexpressed is more likely to be false positive than not.

Working Examples

The specification has one working example in which the nucleic acid may be overexpressed in some tumor samples, but the working example was lacks sufficient information regarding internal controls to show that the protein was, in fact, overexpressed, that the nucleic acid was associated with any disease or that the results are anything other than spurious.

Guidance in the Specification.

The specification, while correlating PRO1800 with Hep 27, did not teach any actual function or use for PRO1800, nor, in fact, any use for Hep 27 itself.

Level of Skill in the Art

The level of skill in the art is deemed to be high.

Conclusion

Thus given the broad claims in an art whose nature is identified as unpredictable, the unpredictability of that art, the large quantity of research required to define these unpredictable variables, the lack of guidance provided in the specification, the presence of a working example which does not address the issue of the efficacy of the control and the negative teachings in the prior art balanced only against the high skill level in the art, it is the position of the examiner that it would require undue experimentation for one of skill in the art to perform the method of the claim as broadly written.

Response to Arguments

6. Applicant's arguments filed May 16, 2005 have been fully considered but they are not persuasive.

Applicant reiterates the arguments made previously.

Prior art arguments

Separately, the examiner incorporates the arguments in response to Applicant in 09/866,034 regarding the prior art issues. Regarding the Lewin reference, as characterized by applicants, the reference teaches "various molecular events that lead of overexpression of a gene product". This argument has been fully considered but is not deemed persuasive because applicants are putting the cart before the horse. The issue here is *not* that a gene product has been found to be overexpressed, and an explanation of such is being sought, but rather that a *mild, two-fold* amplification of the DNA that would be transcribed to mRNA, that would be translated to protein. There is no evidence of record that the protein is present at elevated level, and the art would not lead to that expectation, as evidenced by Pennica. There is no assertion in the specification that a retrovirus has been inserted upstream of the PRO1800 gene, nor would such be consistent with the data in the specification as originally filed. Similarly, there is no evidence of record of a chromosomal translocation, nor of any overexpression of the PRO1800 protein.

At page 11 of the response, Applicants assert that references by Alitalo and Merlino support the assertion that the claimed PRO1800 protein would have diagnostic

utility. As characterized by applicants, "Alitalo teaches gene amplification of oncogenes results in elevated expression of the gene, and that increased dosage of the gene product may contribute to the progression of some cancers." This argument has been fully considered but is not deemed persuasive because once again, applicants are putting the cart before the horse. Alitalo is examining the amplification of *known oncogenes,* whose products were *known* to be overexpressed at the protein level. Further, dmils and HSRs, as discussed by Alitalo, are cytological phenomena. As stated by Alitalo at page 306, "Although the sampling of tumours is at present small, the finding of *known cellular oncogenes* among amplified DNA represented by dmil:s and HSR:s of cancer cells is provocative. Amplification has been found to affect at least five out of twenty *known* cellular oncogenes and the degree of gene amplification varies from *five to many hundred-fold* over the single haploid copies found in normal cells" (emphases added). Thus, Alitalo is discussing *known* oncogene, wherein the DNA is amplified *five to many hundred fold.* PRO1800 is neither a known oncogene, nor amplified five to many hundred fold. There is nothing in Alitalo's disclosure that would lead the artisan to conclude that a gene that is amplified two-fold in some cancers either would be expected to be an oncogene, nor would be expected to be accompanied by an increase in protein levels. With respect to the Merlino publication, EGF, or Epidermal Growth Factor, is a known growth factor. It is known in the art that overexpression of growth factors or their receptors can result in uncontrolled cell growth, one of the hallmarks of cancer. On the contrary, PRO1800 is asserted in the specification to have (unspecified) homology to Hep27, which Hep27 is a member of the short chain alcohol

dehydrogenase protein family (page 2). There is no nexus between short chain alcohol dehydrogenases and cancer, nor is there sufficient similarity between PRO1800 and short chain alcohol dehydrogenase protein family such that the person of ordinary skill in the art would accept the assertion that PRO1800 is a short chain alcohol dehydrogenase. Further, Merlino discloses that the EGF receptor gene was amplified 4-5 fold, not the mere two-fold amplification observed for PRO1800. Further still, the EGF receptor was *known to be overexpressed* in the cell line studied by Merlino. Applicants have provided no evidence of overexpression of the PRO1800 protein in any of the tested cancer cells.

At page 12 of the response, applicants argue that Bahnassy et al. "studied the amplification of *cyclin D1, cyclin A, histone A3* and *Ki-67*", and found "a significant correlation between *cyclin D1* gene amplification and protein overexpression." This argument has been fully considered but is not deemed persuasive. First, based upon applicants argument alone, we may presume that *no* significant correlation was found for the other genes studied, such that taken on applicants characterization alone, there would appear to be only a 25% chance of such a correlation (not that four is a significant sample size). More to the point, however, all four genes were selected by Bahnassy due to their known functions as 'cell cycle checkpoints', i.e. genes that influence the progression of the cell cycle. As cancer is known to be associated with aberrations in regulation of the cell cycle, this was a targeted study, looking at genes *likely* to be associated with cancer. No such association exists for PRO1800. Further, Bahnassy found amplification of the cyclin D1 gene to be 2-10 fold, higher than found

for PRO1800. Finally, the discussion section of the paper clearly indicates that the art at the time the paper was written had *not* found either consistency or consensus on the assertion that amplification of cyclin D1 as associated with increased protein levels. In fact, at page 20, Bahnassy states that "So far, several studies were done to reveal the prognostic significance of cyclin D1 overexpression in various carcinomas, including CRC 1221. However, these studies yielded conflicting results which could be attributed to organ heterogeneity. In our study, patients with tumors that exhibited cyclin D1 overexpression tended to have poor prognosis." In all, Bahnassy shows that far more experimentation is required than is present in this specification as originally filed to establish a correlation between protein expression and cancer in the mind of the skilled artisan, and that the type of experimentation found in the specification as originally filed, in which a mere two-fold amplification of DNA was observed in a few cell lines, and no analysis of protein expression was performed, falls far short of the standard in the art. The Blancato reference, as for Lewin, examined a protein, c-myc, the same as discussed by Lewin, *known* to be associated with cancer. Blancato's starting point was that the protein was known to be overexpressed, and the investigation was aimed at determining the mechanism of overexpression. No such overexpression has been established for PRO1800.

At page 13, applicants argue that it is well known in the art that initiation of transcription is the most common point for a cell to regulate the expression of each of its genes. This argument has been fully considered but is not deemed persuasive because

the amplification of PRO1800 was demonstrated at the DNA level; there has been no examination of transcription levels of the gene, much less amounts of protein.

The Examiner notes additional art that supports the rejection, in that the art indicates that a two-fold amplification at the DNA level would not be expected to be predictive of protein amplification.

Hu et al. (2003, Journal of Proteome Research 2:405-412) analyzed 2286 genes that showed a greater than I-fold difference in mean expression level between breast cancer samples and normal samples in a microarray (p. 408, middle of right column) and discovered that, for genes displaying a 5-fold change or less in tumors compared to normal, there was no evidence of a correlation between altered gene expression and a known role in the disease. However, among genes with a 10-fold or more change in expression level, there was a strong and significant correlation between expression level and a published role in the disease (see discussion section).

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Orntoft et al. (Molecular and Cellular Proteomics1:37-45, 2002) *could only compare the levels of about 40 well-resolved and focused abundant proteins."* (See abstract.) It would appear that applicants have provided no fact or evidence

concerning a correlation between such low levels of amplification of DNA, found only in a minority of tested tumors which were not characterized on the basis of those in the Orntoft publication, and an associated rise in level of the encoded protein.

Hyman (Cancer Research 62:6240-6245) found 44% of *highly* amplified genes showing overexpression at the mRNA level, and 10.5% of *highly* overexpressed genes being amplified; thus, even at the level of high amplification and high overexpression, the two do not correlate. Further, the article at page 6244 states that of the 12,000 transcripts analyzed, a set of 270 was identified in which overexpression was attributable to gene amplification. This proportion is approximately 2%; the Examiner maintains that 2% does not provide a reasonable expectation that the slight amplification of PRO1800 would be correlated with elevated levels of mRNA, much less protein. Hyman does not examine protein expression.

Thus, the preponderance of the art supports the *prima facie* finding that a minor amplification of DNA would not form the basis for a substantial assertion of an association between PRO1800 protein and cancer.

Fundamental Utility Caselaw as applied to PRO1800

First, as discussed previously, in analyzing utility, the first place to begin is with the decision of the Supreme Court in Brenner v. Manson, 383 U.S. 519, 148 USPQ 689 (1966). In Brenner, the Court concluded that "[t]he basic quid pro quo contemplated by the Constitution and the Congress for granting a patent monopoly is the benefit derived by the public from an invention with substantial utility. Unless and until a process is refined and developed to this point-where specific benefit exists in currently available

form-there is insufficient justification for permitting an applicant to engross what may prove to be a broad field." Id. at 534-35, 148 USPQ at 695.

There is no specific benefit, in currently available form, for the Pro-1800 protein and antibody, since there are no specific and substantial utilities for that Pro-1800 protein and antibody.

The CCPA first applied Brenner in In re Kirk, 376 F.2d 936, 153 USPQ 48 (CCPA 1967). The invention claimed in Kirk was a set of steroid derivatives said to have valuable biological properties and to be of value "in the furtherance of steroidal research and in the application of steroidal materials to veterinary or medical practice." Id. at 938, 153 USPQ at 50. The claims had been rejected for lack of utility. In response, the applicants submitted an affidavit which purportedly "show[ed] that one skilled in the art would be able to determine the biological uses of the claimed compounds by routine tests." Id. at 939, 153 USPQ at 51. The court held that "nebulous expressions [like] 'biological activity' or 'biological properties'" did not adequately convey how to use the claimed compounds. Id. at 941, 153 USPQ at 52. Nor did the applicants' affidavit help their case: "the sum and substance of the affidavit appear[ed] to be that one of ordinary skill in the art would know 'how to use' the compounds to find out in the first instance whether the compounds are-or are not-in fact useful or possess useful properties, and to ascertain what those properties are." Id. at 942, 153 USPQ at 53. The Kirk court held that an earlier CCPA decision, holding that a chemical compound meets the requirements of § 101 if it is useful to chemists doing research on steroids, had effectively been overruled by Brenner. "There can be no doubt that the insubstantial,

superficial nature of vague, general disclosures or arguments of 'useful in research' or 'useful as building blocks of value to the researcher' was recognized, and clearly rejected, by the Supreme Court" in Brenner. See Kirk, 376 F.2d at 945, 153 USPQ at 55.

The current situation is identical to that in Kirk. The Declarations filed provide evidence that one could determine whether the Pro-1800 protein is useful, but do not even show any utility specifically for Pro-1800 as discussed above. Further, the discussion cited by Applicant of the various declarations, such as the discussion on page 16 of the response, clearly represent language which is "useful in research" but has no current practical use. The speculation by the Declarants that medical practitioners might wish to know if proteins in general are overexpressed, without reference to Pro-1800 in particular, is precisely the sort of vague argument which lacks any specificity.

There is no particular therapy associated with overexpression of the Pro-1800 protein. There is no particular diagnosis associated with overexpression of the Pro-1800 protein. There is no particular use whatsoever associated with overexpression of the Pro-1800 protein and resultant antibody. There are only vague general statements that such an overexpression might be useful in research or therapy. This is insufficient according the to the Kirk court. This is particularly demonstrated when Applicant argues that the proteins might be useful for tissue typing (see page 17). This is a classic throwaway utility since there is no evidence that Pro-1800 protein is associated with any particular tissue at all.

Similarly, with regard to specific utility, the declaration, the arguments and the specification are entirely silent on any real specific utility for Pro-1800. When Applicant states that evidence of overexpression of PRO1800 nucleic acids provides utility to the protein, this presumes the protein is similarly overexpressed. As discussed at length above, this is not necessarily the case. Consequently, this cannot serve as a foundation stone to support specific utility.

Applicants cited caselaw

Applicant first cites Fujikawa v. Wattanasin for the proposition that utility need be shown only to a "reasonable certainty" and absolute proof is not required. This argument is not persuasive for two reasons. First, as evidenced by the art such as Pennica and Konopka, even if the the "reasonable probability" standard is used, there is no reasonable certainty that a protein will be overexpressed when the nucleic acid is expressed.

Second, and perhaps more importantly, the case is really inapposite to the current situation because the utility question is significantly different. In Fujikawa v. Wattanasin, the question was whether in vitro testing that showed a compound lowered cholesterol provided utility for that compound as confirmed by in vivo testing. In the current case, no in vivo results whatsoever are present. The use of the Fujikawa compound is expressly evident from the results, that is, the compound can be used to treat high cholesterol, and that is the use intended by that applicant. That situation is significantly different from the current case because there is no evidence that the Pro-1800 protein is diagnostic of cancer. Unlike the in vitro testing in Fujikawa v.

Wattanasin, where a positive result provided an indication that the compound was potentially useful in cholesterol lowering, and which result was confirmed by in vivo testing, a positive result of overexpression in lung cancer for the Pro-1800 nucleic acid provides very little information for utility of the nucleic acid. There is no "reasonable probability" that the nucleic acid would be diagnostic of cancer in any way, and significantly less than a "reasonable probability" for the Pro-1800 protein for which no evidence of utility whatsoever is presented. Antibodies to the Pro-1800 protein, which protein has not been shown to be overexpressed in cancer or to have any other use, lack any "reasonable probability" of utility. Consequently, the fact pattern of Fujikawa v. Wattanasin does not apply because the level of certainty in this case is below the "reasonable probability" required by that CAFC in that decision.

This is similar to the cited Cross v. Iizuka case where specific inhibition of thromboxane synthetase was demonstrated for utility of the compounds. This is worlds apart from the current situation where no result whatsoever is shown for the claimed antibodies to Pro-1800. No therapeutic or functional utility is even alleged other than the concept that the antibodies may detect the Pro-1800 protein, for which no evidence of any utility has been provided. The closest asserted utility is for the Pro-1800 nucleic acid, and this utility, for the reasons extensively discussed in the rejection, above and previously, does not carry over into the protein.

The conclusion that is reached is that it is NOT more likely than not that there is a "reasonable probability" that the asserted utility for the antibodies is true.

Nonspecific Arguments

Applicant then cites a series of sources for the entirely nonspecific argument that for some proteins, nucleic acid overexpression is correlated with protein overexpression. As noted in the rejection, there are other articles which demonstrate that there is no necessary relationship for every protein. Nonspecific arguments do not relate to PRO-1800. None of the references demonstrate that there is a "reasonable probability" that the Pro-1800 protein is overexpressed or that antibodies to the Pro-1800 protein itself have any utility.

It is interesting that Applicant relies upon two cases, Fujikawa v. Wattanasin and Cross v. Iizuka, where specific evidence of utility for the specific molecules was presented, but Applicant fails to provide such evidence for Pro-1800 and attempts instead to rely upon other, unrelated proteins. Fujikawa v. Wattanasin and Cross v. Iizuka both seem to stand for the proposition that is consonant with Brenner v. Manson, which is that specific evidence of utility for the specific molecule claimed is required. That specific evidence is absent and the conclusion is inescapable that the antibodies to Pro-1800 therefore lack utility and this conclusion is maintained.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jeffrey Fredman whose telephone number is (571)272-0742. The examiner can normally be reached on 6:30-3:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion can be reached on (571)272-0782. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

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